Claim 36 has been canceled. Appendix A is attached hereto containing a marked-up version of the amended specification and claims, and Appendix B is attached hereto containing a clean set of the pending claims.

B. Objections

Claims 36-38 are objected to under 37 C.F.R. §1.75(c) as being of improper dependent form. The Action asserts that claim 18 is drawn to a method of treating cancer, and that claim 36 is redundant. In response, claim 36 has been canceled. Claims 37 and 38 have been amended to depend from claim 18.

Claim 39 has been objected to under 37 C.F.R. §1.75 as being a substantial duplicate of claim 31. Applicants respectfully traverse. Claim 31 is directed to the method of claim 18, wherein the first and second compositions are contained within a pharmaceutically acceptable composition. Applicants draw Examiner's attention to the fact that claim 18 has been amended to recite first and second compositions, in accordance with the rejection under 35 U.S.C. §112, second paragraph (see below). Claim 39, in contrast to claim 31, is drawn to the method of claim 18, wherein the first and second compositions are combined in a single formulation. Applicants assert that formulating two compositions individually in a pharmaceutically acceptable composition is distinct from formulating the compositions together in a single formulation. In addition, these methods of formulation are sufficiently distinct that they do not claim the same thing.

Claim 47 is objected to as being a substantial duplicate of claim 40. Applicants respectfully traverse. Claim 47 includes the limitation "wherein the composition is a pharmaceutically acceptable composition. Claim 40 does not include this limitation. Therefore,

Applicants assert that claim 47 is narrower than claim 47, and is thus not a substantial duplicate of claim 40 because not every composition is a pharmaceutically acceptable composition. In addition, claims 47 and 40 are not so close in content that they cover the same thing.

Claim 31 is objected to as being a substantial duplicate of claim 18. Applicants respectfully traverse. As noted in regard to claims 47 and 40, claim 31 includes the limitation "wherein said first and second compositions are contained within a pharmaceutically acceptable composition." Claim 18 does not include this limitation. Applicants reassert that not every composition is a pharmaceutically acceptable composition, and that the claims are not so close in content that they cover the same thing.

The Examiner asserts that "without a recitation of a specific limitation of 'pharmaceutically acceptable,' the methods of claim 31 are not patentably distinct from the methods of claim 39 and the products of claim 47 are not patentably distinct from the products of claim 45. Applicants respectfully traverse. Applicants' argument in regards to claims 31 and 39 is set forth above, and Applicants reassert that formulations of claim 39 are patentably distinct from the formulations of claim 31, since the first and second compositions of claim 39 are formulated together, whereas the first and second compositions of claim 31 may be formulated separately. In addition, Applicants traverse the Examiner's assertion that the compositions of claims 47 and 45 are not patentably distinct. Claim 47 includes the limitation "pharmaceutically acceptable composition" whereas claim 45 does not include this limitation. Nor are the claims so close in content as to cover the same thing, since it is clear that not every composition is a pharmaceutical composition.

In view of the above amendments and argument, Applicants respectfully request that these objections should be withdrawn.

C. Rejections Under 35 U.S.C. §112, Second Paragraph

The Action rejects claims 28-35 and 39 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Action, the recitations of "said first composition" and "said second composition" in claim 18 lack antecedent basis. Claim 18 has been amended to include antecedent basis for the terms "said first composition" and "said second composition." In view of this amendment, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

D. Rejections Under 35 U.S.C. §103

The Examiner has made a number of rejections under 35 U.S.C. §103(a). In particular, claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45, and 47 are rejected as being unpatentable over Uckun *et al.* (U.S. Patent No. 6,191,123) in view of Mukhopadhyay *et al.* (U.S. Patent No. 5,958,892). Claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45, and 47 are rejected as being unpatentable over Uckun *et al.* in view of Mukhopadhyay *et al.* and the abstract of Barchowsky *et al.* (Toxicology and Applied Pharmacology, 1999, Vol. 159, pp. 65-75). In addition, claims 1-5, 12, 14-18, 15, 27-40, 45, and 47 are rejected under 35 U.S.C. §103(a) as being unpatentable over Uckun *et al.* in view of Mukhopadhyay *et al.* and the abstract of Barchowsky *et al.* as applied to claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45, and 47, and further in view of the abstract of Oldham *et al.* (Proc. Amer. Assoc. Cancer Res., 2000, Vol 41, p. 766).

According to the Examiner, Uckun *et al.* teaches a method of treating leukemia or breast cancer comprising the administration of an arsenate to a subject, wherein the arsenate induces apoptosis in cancer cells. Mukhopadhyay *et al.* is said to teach a method of treating cancer by administering 2-methoxyestradiol to induce apoptosis in cancer cells. Mukhopadhyay *et al.* is said to also teach a combination regimen for cancer therapy involving 2-methoxyestradiol with at least one chemotherapeutic agent. The Examiner, who admits that neither Uckun *et al.* or Mukhopadhyay *et al.* teaches the combination of 2-methoxyestradiol with an arsenate agent, nevertheless asserts that "it would have been obvious to combine both 2-methoxyestradiol and arsenates for the treatment of solid tumors because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for treating tumors by the induction of apoptosis in tumor cells, and that one of ordinary skill in the art would have been motivated to combine the two agents with a reasonable expectation of success.

Barchowsky *et al.* is said to teach that vascular endothelial cells exhibited increased superoxide and hydrogen peroxide accumulation when exposed to low levels of arsenic, and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer 2-methoxyestradiol and arsenate in a method of treating cancer and killing a cell. The abstract of Oldham *et al.* is purported to teach that 2-methoxyestradiol selectively kills leukemia cells and that this killing is a result of inhibition of SOD by 2-methoxyestradiol, and that SOD is a key enzyme responsible for protecting cells from free-radical damage due to superoxide radicals.

Applicants respectfully traverse these rejections. According to the *Manual of Patent Examining Procedure*, §715.02, Applicants may overcome a 35 U.S.C. §103 rejection based on a

combination of references by showing completion of the invention by Applicants prior to the effective date of any of the references, and that Applicants need not antedate the reference with the earliest effective filing date. Applicants herein submit as Exhibit 1 a declaration under 37 C.F.R. §1.131 which sets forth facts demonstrating that the invention as reflected in the claims was reduced to practice prior to June 23, 1999. The earliest effective date of Uckun *et al.* as a reference is June 23, 1999, its filing date. The earliest effective date of Oldham *et al.* as a reference is March, 2000, its publication date. The earliest effective date of Barchowsky *et al.* as a reference is June, 1999. In addition, Mukhopadhyay *et al.* was available under 35 U.S.C. §102(a)/103(a) as a reference as of its issue date, September 28, 1999. Applicants assert that in view of their antedating declaration, Uckun *et al.*, Oldham *et al.*, and Barchowsky *et al.* are not proper references under 35 U.S.C. §103(a), nor is Mukhopadhyay et al. available as a reference under 35 U.S.C. §102(a)/103.

In view of the above, the only reference that might be available would be Mukhopadhyay *et al.* under 35 U.S.C. §102(e)/103. However, Applicants herein submit a Declaration under 37 C.F.R. §1.132 (Exhibit 2) to demonstrate that this application is subject to an obligation of assignment to the Board of Regents, The University of Texas System, and that Mukhopadhyay *et al.* was subject to an obligation of assignment to the same assignee at the time the invention was made. Therefore, Applicants have overcome Mukhopadhyay *et al.* as a reference under 35 U.S.C. §102(e)/103. In view of these two declarations, Applicants assert that each of the rejections under 35 U.S.C. §103(a) be withdrawn.

Even if, for some reason, the Examiner finds the declarations to be improper (and Applicants assert that the declarations are proper) for whatever reason, Applicants further assert that the rejections under 35 U.S.C. §103(a) can be overcome. In order to establish a *prima facie*

case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* § 2142. *See also In re Vaeck*, 947 F.2d 488, 20 U.S. P.Q. 2d, 1438 (Fed. Cir. 1991).

Applicants assert that the Examiner has failed to meet the initial burden of establishing a *prima facie* case of obviousness because the Examiner has failed to demonstrate a suggestion or motivation to combine the reference teachings for any of the combinations of references. Indeed, the Examiner admits that neither Uckun *et al.* or Mukhopadhyay *et al.* teaches the combination of arsenate with 2-methoxyestradiol. Nor is there a suggestion to combine the teaching of the references. The Examiner appears to be asserting that since both references can be combined, this is sufficient to establish *prima facie* obviousness. However, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The Examiner has failed to demonstrate any desirability of the combination of arsenate with 2-methoxyestradiol in the prior art. In addition, the Examiner has failed to provide any evidence that one of skill in the art would be motivated to make the claimed combination with any reasonable expectation of success.

The Examiner asserts that *prima facie* obviousness has been established for the combination of Uckun *et al.* in view of Mukhopadhyay *et al.* under the type of analysis set forth in *In re Kerkhoven*, 205 U.S.P.Q. 1069 (C.C.P.A., 1980), wherein the court held that it is *prima facie* obvious to combine two compositions, each of which is taught in the prior art to be useful

for the same purpose, in order to produce a third composition that is to be used for the very same purpose, since the idea of combining them flows logically from their having been taught individually in the prior art. The claims at issue in *In re Kerkhoven* pertained to processes for the preparation of detergent compositions, and required no more than the mixing of two conventional detergent compositions. 205 U.S.P.Q. 1070. The C.C.P.A. held that "[i]t is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose, and that "the idea of combining them flows logically from their having been individually taught in the prior art." 205 U.S.P.Q. 1072. The court noted demonstration of superiority of the claimed combination over the prior art's techniques, which appellant failed to prove, would have rebutted the rejection. 205 U.S.P.Q. at 1072-1073.

Applicants assert that even if there was a *prima facie* case of obviousness (which Applicants assert has not been established), it would be successfully rebutted because Applicants' specification provides more than ample evidence of superiority of the claimed composition of an arsenate composition with a 2-methoxyestradiol composition. In particular, the inventors have determined that 2-methoxyestradiol inhibits superoxide dismutase (SOD) and compromises the cell's ability to eliminate superoxide anion, and that the combination of 2-methoxyestradiol with an agent or agents that increases reactive oxygen intermediates within a cell results in an enhanced ability to kill cells, specifically cancer cells. Specification, page 4, lines 3-7; and Examples (see below). While both classes of agents may be used independently as cancer therapeutics, the instant invention discloses that the mechanism-based combination of compounds produces a synergistic effect that dramatically increases the tumoricidal and/or anti-

neoplastic efficacy of each compound. Specification, page 4, lines 7-10; and Examples (see below).

More specifically, Example 1 demonstrates that SOD is a key target of 2-methoxyestradiol in causing apoptosis. Example 2 demonstrates the important role of free radical in mediating the cytotoxic effect of 2-methoxyestradiol, and demonstrates the synergistic effect between 2-methoxyestradiol and ionizing radiation, a known generator of free radicals within cells. Example 3 (and FIGS. 39-40) show that the combination of arsenate, which is thought to contribute to free radicals within cells, with 2-methoxyestradiol substantially increased the cytotoxic activity against primary human leukemia cells from CLL patients *in vitro*. As shown in FIGS. 41-42, the combination of arsenate with 2-methoxyestradiol caused significant loss of viability in the CLL cells, which were insensitive to either drug alone. In addition, Example 3 shows results indicating that the combination of all-trans retinoic acid, which is known to increase cellular free radicals, with 2-methoxyestradiol demonstrated anti-leukemic activity against CLL cells that was clearly more than the additive effect of both compounds. These sections of the specification demonstrate superiority of the claimed combination of an arsenate composition with a 2-methoxyestradiol composition, which Applicants assert is more than sufficient to rebut any *prima facie* case of obviousness based on the analysis of *In re Kerkhoven*.

Applicants assert that, as with the combination of references consisting only of Uckun *et al.* and Mukhopadhyay *et al.*, the Examiner has again failed to establish a *prima facie* case of obviousness using the combinations with the additional references of Barchowsky *et al.* and Oldman *et al.* In particular, the Examiner has failed to demonstrate any suggestion or motivation to combine the reference teachings to practice the claimed invention. Barchowsky *et al.* and

Oldman *et al.* do not provide any suggestion or motivation to combine the reference teachings, and neither provides the information missing in Uckun *et al.* and Mukhopadhyay *et al.* to practice the claimed invention. More specifically, Barchowsky *et al.* and Oldman *et al.* do not provide any information as to the combination of arsenate and 2-methoxyestradiol in cancer therapeutics. The Examiner, without providing rationale, merely asserts that one of skill in the art would have been motivated to practice the claimed invention based on the reference teachings. In effect, the Examiner appears to be relying on the level of skill of one in the art to provide the suggestion to practice the claimed invention. However, the level of skill in the art cannot be relied upon to provide the suggestion to combine the references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

The Examiner has also failed to demonstrate that one of skill in the art would be above to practice the claimed invention based on the teachings of the reference, with any reasonable expectation of success. As noted above, even if the Examiner has established a *prima facie* case of obviousness (which Applicants do not agree is the case), Applicants have successfully rebutted any *prima facie* case by providing ample evidence of superior and unexpected results.

For all of these reasons, Applicants respectfully request that the rejections under 35 U.S.C. §103(a) are overcome.

E. Conclusion

In view of the foregoing, it is believed that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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